Synthesis of Novel 1,2,3,4-Tetrahydroisoquinoline-3-carboxylic Acid Derivatives through the Application of Rongalite: A Synergistic Combination of [2+2+2]- and [4+2]-Cycloaddition Reactions

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Abstract: An efficient route for the synthesis of several novel 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic) derivatives has been reported. A synergistic combination of [2+2+2]- and [4+2]-cycloaddition reactions has been used for the synthesis of the desired targets.

Key words: 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, Rongalite, cycloaddition, amino acids, quinones

1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid (1, Tic; Figure 1) is a constrained analogue of phenylalanine (Phe). The main advantage of constrained amino acids and their derivatives is their stability towards enzymatic degradation. Incorporation of constrained amino acid moieties in a peptide chain can modify the physiological as well as the binding properties of the resulting peptide. In 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, the six-membered heterocyclic ring is formed by incorporation of a methylene unit between the amino group and the aromatic ring of phenylalanine. Since the nitrogen atom in 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid is protected, this type of amino acid can play an important role in the design of peptidomimetics. It was found that the insertion of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid in the second position of an opioid receptor exerts conformational restrictions and results in drastic changes in its intrinsic activity. The tetrahydroisoquinoline unit has been extensively used in peptide-based drugs and, in several instances, it appears to play a crucial role in the design of various lead molecules.

Figure 1

Recently, Lipkowski and co-workers have reported that 6-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (6HTc) can simulate tyrosine conformation in an opioid ligand receptor complex. The tetrahydroisoquinoline unit is also a critical component of inhibitors of phenylalanine N-methyltransferase. Similarly, the 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid unit has also been incorporated in farnesyl transferase inhibitor 3 and its analogues (Figure 2) as a replacement for phenylalanine. Moexipril (2), an ACE inhibitor, contains 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid as a core structural unit (Figure 2). In view of the various applications of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivatives, a need remains for new synthetic strategies. Some of the common methods for the preparation of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid and its derivatives are: Pictet–Spengler reaction, Bischler–Napieralski reaction, or by alkylation strategies. These methods, however, employ a preformed benzene ring derivative as a starting material and they provide limited opportunities for the introduction of diverse functional groups in the benzene ring.

In view of our interest in developing new methodologies for 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid–quinone hybrids via a ‘building block approach’, we sought a general and useful approach based on [2+2+2] cycloaddition and Diels–Alder reactions as key steps. The strategy based on cycloaddition reactions has a unique advantage over existing methods as diverse substituents can be introduced in the aromatic ring by judicious selection of the reacting partners. Although there are several methods available for the construction of tetrahydroisoquinoline units, these strategies cannot easily be extended to 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivatives.

Given the synthetic challenge of developing new strategies to 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivatives, cycloaddition approaches provide a unique advantage in terms of diversification. Unlike other routes, this approach is well suited to the generation of annulated benzene derivatives and it can also be used to generate a library of compounds by varying the reacting partners. The retrosynthetic analysis for 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid based on cycloaddition reactions is shown in Scheme 1.

In view of our earlier experience in generating o-xylylene intermediates under mild reaction conditions, we envisaged that a novel sultine building block 7 would be useful for the synthesis of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid based amino acid derivatives. We preferred sultine 7 as a latent diene intermediate over the other pos-
sible precursors such as benzocyclobutene derivatives because sultine derivatives can be transformed into a highly reactive \(\sigma\)-xyylene intermediate \(6\) under milder conditions by chelotropic elimination of sulfur dioxide.\(^{18}\) The transient diene \(6\) thus generated under thermal conditions is well suited to the Diels–Alder strategy. Herein, we report the realization of the proposed strategy (Scheme 1) for the preparation of various 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid based amino acid derivatives.

The required diol building block \(8\) was prepared by following literature procedure starting from the alkyne building block \(11\), which in turn can be obtained from benzophenone imine.\(^ {19}\) The diol \(8\) was treated with phosphorus tribromide in anhydrous chloroform to generate the corresponding dibromo derivative \(9\) in 83% yield. The formation of \(9\) was confirmed by the disappearance of protons attached to the hydroxy group at \(\delta = 3.76\) and the appearance of the \(\text{CH}_2\text{Br}\) protons at \(\delta = 4.58\) in the high-field \(^1\text{H}\) NMR spectrum. Next, the dibromo derivative was treated with Rongalite (sodium hydroxymethanesulfinate, \(\text{CH}_3\text{NaO}_3\text{S} \cdot 2\text{H}_2\text{O}\)) in the presence of tetrabutylammonium bromide in anhydrous \(\text{N},\text{N}\)-dimethylformamide to give the sultine derivative \(7\) as a mixture of diastereomers. Since the stereochemistry of the sultine is of no consequence in the generation of the \(\sigma\)-xyylene intermediate \(6\), it was not necessary to separate the isomers. Moreover, TLC behavior indicated that the mixtures of isomers would be inseparable by column chromatography. Having the sultine derivative in hand, its Diels–Alder chemistry with various quinone-based dienophiles was undertaken. The sultine derivative was heated at 85–90 °C in the presence of excess dienophiles \(12–16\) to give the Diels–Alder adducts. The Diels–Alder adducts were slightly contaminated with the aromatized product and therefore no attempts were made to isolate the Diels–Alder adducts. Aromatization of the Diels–Alder adducts was achieved using activated manganese dioxide to furnish the 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivatives \(17–21\) (Table 1).

The aromatized products \(17–21\) were characterized based on their spectral data, such as \(^1\text{H}\) and \(^{13}\text{C}\) NMR and HRMS. The mild reaction conditions employed and the
atom economy process involved make this route attractive for the preparation of several previously inaccessible unusual amino acid derivatives embodying the 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid moiety.

We have developed a short and an efficient route for the synthesis of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid–quinone hybrids. We found that a combination of [2+2+2]- and [4+2]-cycloaddition reactions is extremely effective.

Scheme 2  Synthetic approach to highly functionalized 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivatives

Table 1  1,2,3,4-Tetrahydroisoquinoline-3-carboxylic Acid Derivatives Prepared by Diels–Alder Reaction/Aromatization

<table>
<thead>
<tr>
<th>Entry</th>
<th>Dienophile</th>
<th>Aromatized product</th>
<th>Yieldb (%)</th>
</tr>
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<tr>
<td>1</td>
<td></td>
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<td>71</td>
</tr>
<tr>
<td>2</td>
<td></td>
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</tr>
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<td>3</td>
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</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td>70</td>
</tr>
</tbody>
</table>

*Diels–Alder reaction was carried out in toluene at reflux.

*Isolated overall yield after Diels–Alder and aromatization step.
useful for the generation of polycyclic molecules in an efficient and atom-economic manner. Since enantiomerically pure building blocks related to 11 are commercially available, the methodology can easily be adopted for the preparation of optically active 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivatives. We anticipate that the introduction of a variety of quinone moieties in 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid will have impact in medicinal chemistry and also for the design of new peptidomimetics.

All reactions were monitored by TLC carried out on glass plates coated with silica gel GF 254 (containing 13% calcium sulfate as a binder, Acme). Visualization of the spots on TLC plates was achieved either by exposure to I$_2$ vapor or UV light. Flash chromatography was performed using silica gel (100–200 mesh, Acme). The solvent was concentrated under reduced pressure and the crude product thus obtained was purified by column chromatography (silica gel, EtOAc–PE, 3:7) to afford compound 18. The crude product was stirred at r.t. for 6 h. The mixture was then poured into ice-cold H$_2$O (40 mL) and extracted with CHCl$_3$ (3×50 mL). The combined organic extracts were dried (MgSO$_4$) and concentrated under reduced pressure to give a crude product that was purified by column chromatography (silica gel, EtOAc–PE, 3:7) to afford 17 as a yellow crystalline solid; yield: 11 mg (71%); mp 170–172 °C (dec.); $R_f$ = 0.35 (silica gel, EtOAc–PE, 3:7).

HRMS (Q-TOF): $m/z$ [M + H]$^+$ calcd for C$_{29}$H$_{28}$NO$_6$S: 518.1324; found: 518.1325.

Ethyl 7,10-Dioxo-2-tosyl-1,2,3,4,7,10-hexahydronaphtho[2,3-g]isoquinoline-3-carboxylate (17); Typical Procedure

1,4-Benzoxazine (12, 6 mg, 0.06 mmol) was added to a solution of the sultine 7 (14 mg, 0.03 mmol) in anhyd toluene (5 mL) and the mixture was stirred at reflux for 30 h and then filtered through a Celite pad. The residue was washed with di­oxane (3×5 mL) and the solvent was removed from the washings under reduced pressure to give a crude product that was purified by column chromatography (silica gel, EtOAc–PE, 3:7) to afford 17 as a yellow crystalline solid; yield: 11 mg (72%); mp 178–180 °C (dec.); $R_f$ = 0.30 (silica gel, EtOAc–PE, 3:7).

HRMS (Q-TOF): $m/z$ [M + H]$^+$ calculated for C$_{32}$H$_{24}$NO$_6$S: 490.1324; found: 490.1325.

UV (CHCl$_3$): $\lambda_{\text{max}}$ (e) = 240 nm (11428).

Ethyl 8,9-Dimethyl-7,10-dioxo-2-tosyl-1,2,3,4,7,10-hexahydronaphtho[2,3-g]isoquinoline-3-carboxylate (18)

According to the typical procedure using 2,3-dimethyl-1,4-benzo­quinone (13, 6 mg, 0.04 mmol) and sultine 7 (13 mg, 0.03 mmol) at 90 °C for 12 h, followed by aromatization with activated MnO$_2$ (200 mg, 2.29 mmol) at reflux for 30 h; purification by flash column chromatography (silica gel, EtOAc–PE, 3:7) afforded 18 as a yellow crystalline solid; yield: 11 mg (72%); mp 178–180 °C (dec.); $R_f$ = 0.30 (silica gel, EtOAc–PE, 3:7).

IR (neat): 1731 (ester C=O), 1644 cm$^{-1}$ (ArC=O).

UV (CHCl$_3$): $\lambda_{\text{max}}$ (e) = 240 nm (11428).

Ethyl 8,9-Dimethyl-7,10-dioxo-2-tosyl-1,2,3,4,7,10-hexahydronaphtho[2,3-g]isoquinoline-3-carboxylate (18)

According to the typical procedure using 2,3-dimethyl-1,4-benzoxazine (12, 6 mg, 0.06 mmol) and sultine 7 (13 mg, 0.03 mmol) at 90 °C for 12 h, followed by aromatization with activated MnO$_2$ (200 mg, 2.29 mmol) at reflux for 30 h; purification by flash column chromatography (silica gel, EtOAc–PE, 3:7) afforded 18 as a yellow crystalline solid; yield: 11 mg (72%); mp 178–180 °C (dec.); $R_f$ = 0.30 (silica gel, EtOAc–PE, 3:7).

IR (neat): 1731 (ester C=O), 1644 cm$^{-1}$ (ArC=O).

UV (CHCl$_3$): $\lambda_{\text{max}}$ (e) = 240 nm (11428).
Ethyl 7,12-Dioxo-2-tosyl-1,2,3,4,7,12-hexahydroanthra[2,3-g]isoquinoline-3-carboxylate (19)

According to the typical procedure using 1,4-naphthoquinone (14, 7 mg, 0.04 mmol) and sulphone 7 (14 mg, 0.03 mmol) at 90 °C for 24 h, followed by aromatization with activated MnO₂ (250 mg, 2.87 mmol) at reflux for 30 h; purification by flash column chromatography (silica gel, EtOAc–PE, 3:7) afforded 19 as a yellow crystalline solid; yield: 13 mg (77%); mp 205–207 °C (dec.).

IR (neat): 1729 cm⁻¹ (ester C=O).

1H NMR (300 MHz, CDCl₃): δ = 8.83 (s, 2 H, ArH), 8.93 (s, 1 H, ArH), 8.94 (s, 1 H, ArH), 7.71–7.86 (m, 6 H, ArH), 8.12–8.14 (m, 2 H, ArH), 8.74 (s, 2 H, ArH).

13C NMR (100.6 MHz, CDCl₃): δ = 134.02, 134.07, 134.1, 134.4, 134.60, 134.64, 135.8, 144.0, 170.3, 172.9, 218.6, 233.2.

HRMS (Q-TOF): m/z [M + H]^+ calc for C₃₂H₂₅NO₈S: 554.1461; found: 554.1461.

UV (CHCl₃): λₘₚ (c) = 298 nm (11419).

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References


